PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HRW/42197		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02923	28/07/2000	28/07/1999
International Patent Classification (IPC) or national classification and IPC C07K14/47		
Applicant STOTT, Kelvin		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/01/2001	14.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02923

I. Basis f the rep rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-58 as originally filed

Claims, No.:

1-43 as received on 10/08/2001 with letter of 10/08/2001

Drawings, sheets:

1/5-5/5 as originally filed

Sequence listing part of the description, pages:

1-2, filed with the letter of 10.8.1

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-43
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-43
Industrial applicability (IA)	Yes:	Claims	1-22, 25, 26, 28, 30, 32, 33, 35, 37-41
	No:	Claims	23, 24, 27, 29, 31, 34, 36, 42 and 43

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. Reason d statement on Novelty, Inventive Step and Industrial Applicability

The documents mentioned in the present written opinion / International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- **Novelty (Art.33(2) PCT)**

D2 discloses ligands consisting of D-amino acids for preventing the formation of amyloid-like fibres. The D-amino acids were used to confer resistance to proteolysis, since proteolytic enzymes are not capable of cleaving hydrolyzing peptide bonds between amino acids in D-configuration. On p.12603 (col.2), it was stated that when the utilized D-pentapeptides were incubated alone, no detectable polymers or aggregates were formed. It was further recognized that high content of hydrophobic residues facilitates passage through the blood-brain barrier (p.12605). The peptides used did not have Nα-substituted residues and are hence not relevant to the assessment of novelty.

D3 discloses various modulators of amyloid aggregation. The cores of the modulators consist of beta-sheet forming peptides matching e.g. the beta-sheets of natural beta-amyloid peptides. To the core is attached a modifying group which serves to inhibit aggregation of natural beta-amyloid peptides. The core peptides may consist entirely of D-amino acids (see top p.17) and the peptides may further be derivatized in various ways (for example, peptidic compounds where the peptide backbone has been modified with, for example, methylated amide linkages (p.16, l.32). Further examples of backbone modifications are given on p.17, l.12-14. The modifying group(s) are chosen such that the compound alters aggregation. On p.28, l.18-20, it is suggested that the modifying group can have N-methyl peptide bonds to introduce additional steric hindrance to the aggregation of natural beta-AP. It is however not suggested to add such groups to the core peptide structure. The disclosure of D3 does not clearly combine a core region consisting of D-amino acids and Nα substituted D-amino acids within this core. Hence, D3 cannot be considered to anticipate any of the present claims.

D4 discloses compounds for inhibiting beta-sheet fibre formation in e.g.

Alzheimers (see p.30 for list of conditions). The compounds consist of two beta-sheets linked by a synthetic reverse-turn structure. The two sheets, comprising of a recognition strand and a blocking strand are positioned in a parallel fashion due to the turn. The recognition sequence includes at least one N-methylated residue adjacent to an intramolecularly hydrogen-bonded residue so that it points towards the solvent, not the other strand (see structures on p.26-). The N-methylated residues inhibit oligomerization of the mimetic with itself (see p.18, l.18-23). The blocking strand may also be N-methylated. The amino acids in both strands can be either all L-amino acids or all D-amino acids (p.23, l.6-7).
The rewording of claim 1 has rendered the claims novel over D4, since the Nalpha-substituted residues are found on the binding edge in D3.

D5, which is from the same author as D4, provides the detailed scientific background behind parallel beta-sheet structures such as in D4. Does however not mention D-amino acid use.

- **Inventive Step (Art.33(3) PCT)**

Presently some of the claims lack the essential features of the invention i.e. that the Nα-substitutions cause sufficient steric hindrance to prevent self-aggregation on Nα-substituted edge of peptides (it seems that the peptides could still dimerize by interaction between respective target binding "first edges" anyway) - thus could have small substitutions which do not have this effect and do not solve any problem. Further, the concept of using Nα-substitutions to prevent self-aggregation is documented in D4, D5 and D6. The concept is clearly applicable to D-amino acid sheets (see D4) and it is irrelevant what functional groups are added thereto (unless applicant can demonstrate a surprising effect in the combination of this concept with a particular functional group). Hence, none of present claims considered inventive.

- **Industrial Applicability (Art.33(4) PCT)**

For the assessment of the present claims 23, 24, 27, 29, 31, 34, 36, 42 and 43 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as

industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 23, 24, 27, 29, 31, 34, 36, 42 and 43 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VI. Certain documents

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

D1: WO-A00/52048 (Publication date, 08.09.00; Priority date, 04.03.99; Filing date, 03.03.00)

This document relates to modulators of beta-amyloid peptide aggregation. The modulators may consist of D-amino acids which may have Nα-substitutions. These substitutions have however not been made to specifically address problem of self-aggregation and no indication is given to have these substitutions spread along one side of the β-strand (i.e. separated by odd number of residues). Since D1 is entitled to earlier priority than the present application, the contents of D1 are relevant to the assessment of novelty under Art.54(3), EPC, should the application enter a European Regional Phase. Applicant is requested to address this issue before doing so by removing any overlapping subject-matter.

VIII. Certain observations

- Clarity (Art.6 PCT)

Claim 25 - "..., or comprising a component which mimics the structure and action of said beta-strand-forming section of peptide..." needs to be removed since it is technically not defined and potentially extends the claim beyond matter having the

essential technical features of the invention. Further, is indistinguishable from prior art (e.g. D3) where modulators may have same function and thus be considered to mimic activity of applicants compounds.

Claim 7 - define beta-sheet propensity

It is noted that claims 28, 30, 32, 33, 35, 37, 38 appear to have been drafted as European Style second medical use claims. However, such claims must refer to specific diseases to be treated, not mechanisms of treatment. Hence, these claims would be objected to should applicant enter a regional European Phase.

Claims

1. A chemical compound or composition comprising a peptide, which peptide comprises a β-strand-forming section of peptide which forms a β-strand and associates as such with a target β-strand formed by a separate peptide-containing molecule, or comprising a component which mimics the structure and action of said β-strand-forming section of peptide, wherein the β-strand-forming section of peptide comprises a sequence of at least four consecutive α-D-amino-acid residues, all of which sterically permit the β-strand-forming section of peptide to form a β-strand, and at least one of which is an Nα substituted α-D-amino-acid residue, and any two successive Nα-substituted α-D-amino-acid residues are separated by an odd number of consecutive Nα-unsubstituted α-D-amino-acid residues.

2. A chemical compound or composition according to claim 1, wherein no two successive Nα-substituted amino-acid residues in the β-strand-forming section of peptide are separated by more than 3 consecutive Nα-unsubstituted amino-acid residues.

3. A chemical compound or composition according to claim 1 or claim 2 wherein successive Nα-substituted α-D-amino-acid residues in the β-strand-forming section of peptide are separated from each other by single Nα-unsubstituted α-D-amino-acid residues, such that the β-strand-forming section of peptide comprises an alternating sequence of Nα-substituted and Nα-unsubstituted α-D-amino-acid residues.

4. A chemical compound or composition according to any preceding claim wherein the Nα-substituent of each Nα-substituted α-D-amino-acid residue in the β-strand-forming section of peptide sterically allows or promotes the β-strand-forming section of peptide to form a β-strand, and

sterically hinders the association of one edge of that β-strand with another β-strand.

5. A chemical compound or composition according to claim 4, wherein the Nα-substituent of each Nα-substituted α-D-amino-acid residue in the β-strand-forming section of peptide is selected form the group consisting of:

a fluorine atom or an OH group;

a group that is connected to the Nα atom by an oxygen atom within it;

a group that is connected to the Nα atom by a CH_2 subgroup within it;

a methyl or ethyl group, or some other alkyl or aliphatic group;

a substituted or unsubstituted benzyl group, or some other arylmethyl group;

an acetylated or acylated 2-hydroxy-4-methoxybenzyl (AcHmb) group; and

an acylated or unacylated 2-hydroxybenzyl (AcHb/Hb) group.

6. A chemical compound or composition according to any preceding claim, wherein the side chain of each α-D-amino-acid residue in the β-strand-forming section of peptide allows or promotes the β-strand forming section of peptide to form a β-strand.

7. A chemical compound or composition according to claim 6, wherein the side chain of one or more α-D-amino-acid residues in the β-strand forming section of peptide is that of an amino-acid residue having a β-sheet propensity of greater than 1.00.

8. A chemical compound or composition according to claim 6 or claim 7, wherein the side chain of any one or more α-D-

amino-acid residues in the β-strand forming section of the peptide is selected from the group consisting of:

an atom or group that allows or promotes the β-strand-forming section of peptide to associate as a β-strand with the target β-strand and thereby form a stable β-sheet complex; and

an atom or group that forms a hydrophobic or electrostatic interaction, hydrogen bond, or other favourable non-covalent interaction with the neighbouring side chain of the target β-strand in a β-sheet complex comprising the target β-strand and the β-strand-forming section of peptide.

9. A chemical compound or composition according to any one of claims 6 to 8, wherein the side chain of any one or more α-D-amino-acid residues in the β-strand-forming section of peptide is selected from the group consisting of:

a hydrophobic group, or a group that has a considerable hydrophobic portion;

a branched or unbranched alkyl or aliphatic group;

a group that is branched at its connecting β-carbon atom;

an aromatic group;

an acidic or basic group; and

an amide- or hydroxyl-containing group.

10. A chemical compound or composition according to any preceding claim, wherein the side chain of one or more α-D-amino-acid residues in the β-strand-forming section of peptide hinders the stacking of β-sheets.

11. A chemical compound or composition according to claim 10, wherein the side chain of one or more α-D-amino-acid residues in the β-strand-forming section of peptide extends beyond the neighbouring side chains in the β-strand.

12. A chemical compound or composition according to any preceding claim, wherein the side chain of one or more α-D-amino-acid residues in the β-strand-forming section of peptide allows the compound or composition to be traced or detected.

13. A chemical compound or composition according to claim 12, wherein the side chain of one or more α-D-amino-acid residues in the β-strand-forming section of peptide is selected from the group consisting of:

an atom or group that contains a radioactive or magnetically active nucleus;

that of phenylalanine or tyrosine with one or more radioactive or magnetically active iodine or other halogen atoms substituted onto the aromatic ring;

a fluorescent, coloured, or other spectroscopically detectable group;

a group which contains an unpaired electron and thereby acts as a spin label;

a group which contains the 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) group; and

a group which contains the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) group.

14. A chemical compound or composition according to any preceding claim, wherein the side chain of one or more α-D-amino-acid residues in the β-strand-forming section of peptide is selected from the group consisting of the side chain of:

any naturally occurring α-L-amino-acid or synthetic derivative thereof; glycine; alanine; serine; cysteine; threonine; valine; leucine; isoleucine; methionine; phenylalanine; tyrosine; tryptophan; glutamine; asparagine; glutamate; aspartate; histidine; lysine; arginine; and

tert-leucine or β-hydroxyvaline.

15. A chemical compound or composition according to any preceding claim wherein the target β-strand is formed by the Alzheimer's Aβ peptide, and the β-strand-forming section of peptide binds specifically as a β-strand to part or all of the KLVFFAE sequence within the target β-strand in the parallel orientation, thereby forming a parallel β-sheet complex wherein consecutive residues of the β-strand-forming section of peptide lie diagonally opposite consecutive residues of the KLVFFAE sequence in the same order.

16. A chemical compound or composition according to any one of claims 1 to 14 wherein the target β-strand is formed by the Alzheimer's Aβ peptide, and the β-strand-forming section of peptide binds specifically as a β-strand to part or all of the KLVFFAE sequence within the target β-strand in the antiparallel orientation, thereby forming an antiparallel β-sheet complex wherein consecutive residues of the β-strand-forming section of peptide lie diagonally opposite consecutive residues of the KLVFFAE sequence in reverse order.

17. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide is preceded by, followed by, or otherwise attached to a distinct membrane-penetrating section of peptide which enables the β-strand-forming section of peptide to cross biological barriers such as cell membranes and the blood-brain barrier.

18. A chemical compound or composition according to claim 17 wherein the side chain of each residue in the membrane-penetrating section of peptide is selected from the group consisting of:

a basic or hydrophobic group; and a side chain of alanine, valine, leucine, isoleucine, methionine,

phenylalanine, tyrosine, tryptophan, proline, histidine, lysine, or arginine.

19. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide has a free or acylated N terminus and a free, amidated, or esterified C terminus, or forms part of a larger peptide which has a free or acylated N terminus and a free, amidated, or esterified C terminus.

20. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide is attached to another functional component.

21. A chemical compound or composition according to claim 20, wherein the functional component is selected from the group consisting of:

a component which strengthens the binding of the β-strand-forming section of peptide to the target β-strand;

a component which enhances specificity of association of the β-strand-forming section of peptide with the target β-strand;

a component which enables the β-strand-forming section of peptide to cross biological barriers such as cell membranes and the blood-brain barrier;

a component which causes the compound/composition to target specific organs, cells, or molecules;

a component which allows the compound/composition to be traced or detected;

an atom or group that contains a radioactive or magnetically active nucleus;

a fluorescent, coloured, or other spectroscopically detectable group;

a group which contains an unpaired electron and thereby acts as a spin label;

a group which contains the 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) group or the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) group;

a solid matrix, resin, or support;

an enzyme, hormone, antibody, transcription factor, or other protein molecule;

a group that binds specifically to a particular protein; and

a cytotoxic molecule.

22. A chemical compound or composition according to claim 20 or claim 21, wherein attachment of the β-strand-forming section of peptide to the functional component is by means of an amide or ester linkage formed with the C-terminal carboxyl group or N-terminal amino group of the full peptide, or with a carboxyl, amino, or hydroxyl group of a side chain within the full peptide, or by means of a disulphide bridge formed with a thiol group of a side chain within the full peptide.

23. A method for inhibiting or reversing the association of a target β-strand into a β-sheet or β-fibre, comprising exposing the target β-strand to a chemical compound or composition according to any preceding claim and allowing or inducing the chemical compound or composition to associate with the target β-strand.

24. A method for inhibiting or reversing the aggregation of proteins or peptides, comprising contacting the proteins or peptides with a chemical compound or composition according to any one of claims 1 to 22.

'ATENT COOPERATION TR TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WAKERLEY, Helen, Rachael
Reddie & Grose
16 Theobalds Road
London WC1X 8PL
ROYAUME-UNI

Date of mailing (day/month/year)	
05 April 2001 (05.04.01)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
HRW/42197	
International application No.	**International filing date** (day/month/year)
PCT/GB00/02923	28 July 2000 (28.07.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
STOTT, Kelvin 7 Garrett Road Wokingham Berks. RG40 4RX United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
STOTT, Kelvin 2 Edward Mews Regents Park London NW1 4AT United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 March 2001 (28.03.01)	
International application No. PCT/GB00/02923	**Applicant's or agent's file reference** HRW/42197
International filing date (day/month/year) 28 July 2000 (28.07.00)	**Priority date** (day/month/year) 28 July 1999 (28.07.99)
Applicant STOTT, Kelvin	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 January 2001 (23.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

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